REMARKS

Prior to submission of this amendment, claims 1-99 were pending. Claims 2, 9-13, 21-22, 24-48, 59, and 65-93 have been withdrawn pursuant to the restriction requirement. Claims 3, 11, 15, 23, 50, 58, 94-97, 99, and 105-106 have been canceled. Claims 1, 14, 49, 57, and 98 have been amended to recite that the method is a method of increasing performance gain during treatment or rehabilitation of a cognitive deficit whereby a performance gain is achieved relative to the performance of said cognitive task achieved by training alone. Support for this amendment can be found in claims 3, 15, 50, 58 and 99. Claims 1, 14, 49, 57, and 98 have also been amended to recite that the augmenting agent is a phosphodiesterase inhibitor. Support for this amendment can be found in claims 94-97 and 105-106. No new matter is added by these amendments. Entry of the amendments is requested. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Rejection under 35 U.S.C. 103(a)

The Office Action does not specify which rejections are maintained. The Office Action simply provides a response to arguments made by applicants. If this rejection is maintained, the Examiner is asked to clarify the rejection and specify the references being applied to each rejection.

A) Takayama et al., Katzung, Tully et al, Clavanio and the Merck Manual

The Office Action states that the teachings of Takayama et al., and Katzung that phosphodiesterase inhibitors are useful in the treatment of stroke and the extrinsic teachings in Merck that it is well known in the art to treat stroke victim early, allegedly obviates Applicants claims. As the claims are drafted, the patient is an individual suffering from a stroke. Such a patient would allegedly be on medication as soon as possible and be given therapy as early as possible.

This rejection is traversed for the following reasons.

Applicants have amended the claims to recite a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder or condition in an animal in need of said treatment comprising the steps of: (a) administering to said animal an augmenting agent which enhances CREB pathway function wherein said augmenting agent is a phosphodiesterase inhibitor; and (b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said central nervous system disorder or condition, wherein a performance gain is achieved relative to the performance of said cognitive task achieved by training alone.

As the Examiner is aware there are three requirements to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999) Moreover, the prior art must suggest the specific modification that is necessary in order to arrive at the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990), cert. denied, 498 U.S. 920 (1990).

Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 ("Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure.").

And third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, Applicants submit that the prior art references alone or in combination fail to teach or suggest the claimed invention. The claimed invention is directed to a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder or condition in an animal in need of said treatment comprising the steps of: (a) administering to said animal an augmenting agent which enhances CREB pathway function wherein said augmenting agent is a phosphodiesterase inhibitor; and (b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said central nervous system disorder or condition, wherein a performance gain is achieved relative to the performance of said cognitive task achieved by training alone.

Takayama et al.

Takayama et al., is cited by the Examiner as teaching that "phosphodiesterase inhibitors are useful in the treatment of stroke". Although Takayama et al. teach the use of phosphodiesterase inhibitors in the treatment of the stroke episode, the reference does not teach of suggest the administration of phosphodiesterase inhibitors during the training stage. Nor does Takayama et al. teach or suggest that the administration of the phosphodiesterase inhibitors during or before training will result in performance gain during said treatment as compared to training in the absence of the phosphodiesterase inhibitors.

Katzung

Katzung is cited by the Examiner as teaching that "phospohdiesterase inhibitors are useful in the treatment of stroke". However, this statement is incorrect. In fact, what Katzung states on page 195 is that "Drugs that inhibit phosphodiesterases, the family of enzymes that inactivate cAMP and cGMP, have long been used in ***therapy of heart failure***" (emphasis added).

Heart failure is not stroke. Accordingly, reliance on this reference is misplaced. Withdrawal of the rejection based on Katzung is respectfully requested.

Tully et al.

Tully teach methods of modulating long term memory based on differential regulation of CREB activators and CREB repressors but do not teach or suggest the specific use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke.

Calvanio et al.

Calvanio et al., was cited as teaching "the benefits of training to stroke patients", specifically that "learning can be accelerated and produce a higher level of outcome" "by detecting and controlling attaentional functioning in specific tasks". Calvanio et al discuss various training procedures for stroke survivors, but do not teach or suggest combining training with administration of phosphodiesterase inhibitors.

None of the cited references, alone or in combination, would have suggested to one of ordinary skill in the art at the time the invention was made, that the administration of phosphodiesterase inhibitors at or during training would result in increasing performance gain during treatment of the stroke. Although Takayama et al., teach the use of phosphodiesterase inhibitors in the treatment of the stroke episode, Takayama et al do not teach or suggest training of stroke victims. Takayama et al does not teach or suggest the administration of phosphodiesterase inhibitors during training or that administration of phosphodiesterase inhibitors during training will improve the performance gain achieved during training. Katzung does not teach anything about stroke. Tully does not teach or suggest the use of phosphodiesterase inhibitors in the treatment of stroke or during training. Tully et al, does not teach or suggest that administration of phosphodiesterase inhibitors with training will improve performance gain achieved during training. Calvanio et al. provide training protocols but does not teach the administration of phosphodiesterase inhibitors. Accordingly, one skilled in the art

would not be motivated by the references alone or in combination to combine the administration of phosphodiesterase inhibitors with training.

Secondly, one skilled in the art would not have a reasonable expectation that performance gain could be achieved during training by the administration of phosphodiesterase inhibitors before or with training as compared to training in the absence of phosphodiesterase inhibitors. Nothing in the references teaches or suggests this result.

The Examiner cites Merck that a stroke patient would be on medication as soon as possible and be given therapy as early as possible.

As indicated above, in order to render the claimed invention obvious, there must be a teaching in the art of all of the elements of the claim, motivation in the art to combine the references and a reasonable expectation of success. The claimed invention is now directed to a method of enhancing performance gain during training by the administration of phosphodiesterase inhibitors. The Merck Manual teaches that training should occur. However, it does not teach or suggest that performance gain can be enhanced by the administration of phosphodiesterase inhibitors. Absent such a suggestion or a reasonable expectation of success, this rejection is improper.

In view of these reasons, withdrawal of this rejection is respectfully requested.

B) Christensen IV and the Merck Manual

Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Christensen IV et al., (5,547,979) in view of the Merck Manual.

The Office Action states that Christensen IV et al., allegedly teaches rolipram at column 11, line 14 to column 12, line 14 and in claim 1 claims rolipram in a method of treating stroke. The difference between this reference and Applicants' claims is allegedly the administration of

the compound in conjunction with a training protocol. However, the skilled artisan would allegedly have been motivated to administer this anti-stroke medication in conjunction with a training protocol since Merck Manual at pages 1455 and 1456 teach that a training protocol should be started as early as possible towards a patients rehabilitation.

This rejection is traversed for the following reasons.

Applicants have amended the claims to recite a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder or condition in an animal in need of said treatment comprising the steps of: (a) administering to said animal an augmenting agent which enhances CREB pathway function wherein said augmenting agent is a phosphodiesterase inhibitor; and (b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said central nervous system disorder or condition, wherein a performance gain is achieved relative to the performance of said cognitive task achieved by training alone.

As the Examiner is aware there are three requirements to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999) Moreover, the prior art must suggest the specific modification that is necessary in order to arrive at the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990), cert. denied, 498 U.S. 920 (1990).

Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531

("Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure.").

And third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, Applicants submit that the prior art references alone or in combination fail to teach or suggest the claimed invention. The claimed invention is directed to a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder or condition in an animal in need of said treatment comprising the steps of: (a) administering to said animal an augmenting agent which enhances CREB pathway function wherein said augmenting agent is a phosphodiesterase inhibitor; and (b) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said central nervous system disorder or condition, wherein a performance gain is achieved relative to the performance of said cognitive task achieved by training alone

Christensen IV

Christensen IV et al., teaches the treatment of the stroke episode by administering an effective 'TNF inhibiting amount" of a compound. Christensen teaches that TNF has pro-inflamatory activities which together with its early production make it a likely mediator of tissue injury in several disorders including stroke (col. 6) Christensen does not teach that the compounds are phosphodiesterase inhibitors. Christensen IV do not teach or suggest the administration of the compounds during training. Christensen IV does not teach or suggest that one could achieve performance gain during training by the administration of phosphodiesterase inhibitors before or during training.

The Merck Manual

The Merck Manual teaches training of patients suffering from stroke. The Merck Manual does not teach or suggest the administration of phosphodiesterase inhibitors before or during training. The Merck Manual does not does not teach or suggest that one could achieve performance gain during training by the administration of phosphodiesterase inhibitors before or during training.

Absent a teaching or suggestion in the references either alone or in combination to administer phosphodiesterase inhibitors before or during training, the claimed invention is not rendered obvious. Furthermore, one skilled in the art would not have a reasonable expectation of obtaining a performance gain by the administration of phosphodiesterase inhibitors before or during training as compared to training in the absence of phosphodiesterase inhibitors. In the absence of such a reasonable expectation of success, the invention is non-obvious.

In view of these reasons, withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. 112, first paragraph (enablement)

Claims 97 and 106 stand rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for compounds rolipram and iso-buto-metho-xanthine, does not reasonably provide enablement for "a phosphodiesterase as an augmenting agent" the generic language of claim 97 and 106.

The Office Action states that there are a multitude of phosphodiesterase inhibitors with varying structures, reactivities and bioavailabilities which differ from rolipram and IBMX. Relatively non-selective phosphodiesterase inhibitors include the minor stimulant caffeine and the bronchodilator theophylline. Sildenafil, tadalafil and vardenafil are allegedly selective inhibitors of type V phosphodiesterase (PDE5) which is a cGMP specific. Enoximone, which inhibits PDE IV and milrinone which inhibits PDE IIIc are allegedly useful for the short-term treatment of cardiac failure.

First Applicants note that the Patent Office makes this rejection without providing any support for the statements that these listed compounds are phosphodiesterase inhibitors. Accordingly, the Patent Office has not met its burden of proof. Withdrawal of the rejection on this basis is requested.

Secondly, the test for enablement entails an analysis of whether one skilled in the art is able to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see In *re Wands,* 858 F.2d 731, 8 USPQ 2d 1400, [Fed. Cir. 1988]). A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance provided in the specification, and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "[l]imitations and examples in the specification do not generally limit what is covered by the claims" (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 197 1), cert. denied, 404 U.S. 10 18, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972).

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Proper application of the legal standard must lead to the conclusion that all claims pending in this application are fully enabled.

The specification teaches an augmented cognitive training method which comprises a specific cognitive training protocol and administration of an augmenting agent which is a phosphodiesterase inhibitor. The specification teaches that this combination can improve the efficiency of existing cognitive training protocols because the combination can reduce the number of training sessions required to yield a performance gain or by requiring shorter or no rest intervals between training sessions to yield a performance gain (see e.g. page 2, line 27 to page 3, line 3).

Various training protocols were known in the art. The specification at page 12, line 14 to page 14, line 7 provides a number of references listing such protocols. Therefore one skilled in the art would be able to conduct the training protocols.

The specification provides specific examples of phosphodiesterase inhibitors including rolipram and IBMX (page 18, lines 26-28). One skilled in the art could readily determine whether other compounds were phosphodiesterase inhibitors which could be employed in the claimed methods.

One skilled in the art could readily test a phosphodiesterase inhibitor to determine whether it resulted in performance gain in training when compared to training in the absence of the phosphodiesterase inhibitor. As the Examiner knows, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Accordingly, there is adequate information provided in Applicants specification to enable one skilled in the art to perform the claimed invention.

Withdrawal of this rejection is respectfully requested.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **43373-0008**.

Respectfully submitted,

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